model developed by Shannon et al. in our laboratory, and includes a subsarcolemmal compartment (in addition to the other two commonly formulated cytosolic compartments, junctional and bulk) where the ion channels sense ion concentrations that differ from the bulk. Ion channels and transporters have been modeled on the basis of the most recent experimental data obtained in our group and from the literature. In particular, novel formulations of the rapidly and slowly inactivating components of Ito have been implemented and utilized to differentiate between endocardial and epicardial myocytes. The model has been validated against a wide set of experimental data including action potential adaptation and restitution properties, frequency dependent inotropy and intracellular sodium staircase. It also correctly predicts the effect of pharmacological intervention on K currents (e.g. chromanol 293 B and dofetilide administration) on ventricular repolarization. We conclude that this model is more robust than previously existing models and provides a useful framework to explore excitation-contraction coupling mechanisms and repolarization abnormalities at the single cell level. To overcome the substantial limitations to experimental studies involving human cardiac tissue, due to its low computational cost this model is suitable to be integrated into multi-scale models of tissue and/or heart.

3433-Pos Board B480

Ventricular reentrant arrhythmia due to regional differences - A computational Study

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For many years the most accepted hypothesis is the mechanism of fibrillation in turn leads to arrhythmia was that the anatomical and electrophysiological heterogeneity in cardiac tissue. Regional differences in action potential duration (APD) and changes in depolarization in the heart favor re-entrant arrhythmia. With the help of mathematical model of ventricle cell, the role of sodium on 2D grid of cells in establishing arrhythmia is studied. First a homogeneous tissue of 60×60 was considered with all the parameters are identical. Next the heterogeneity in the tissue has been formed with the help of small squares by varying sodium conductance (g_{Na}) values from its nominal. Also spatial heterogeneity in the tissue has been formed by setting g_{Na} values of some of the squares at deviated values from its nominal. Due to heterogeneity among the cells in the tissue, the action potential (AP) propagation in the tissue is totally arrhythmic. The regional variation in g_{Na} at the center square showed that cells in that region where g_{Na} is varied gets disturbed (i.e. not able to depolarize). Next study, the regional differences in g_{Na}[[Unsupported Character - Codename]] is increased to three squares in diagonal wise. It is observed that the activity pattern of AP propagation in the tissue almost gets disturbed and spiral waves start originating from the center of the squares. Next analysis the number of squares increased to five. Compared to all previous cases, the variation in activity pattern of AP is totally gets collapsed in this case. Further, it is observed that multiple spirals are formed in the tissue around the region where regional differences are made. This multiple spirals further propagated to the entire tissue and causes re-entrant arrhythmia.

3434-Pos Board B481

Drug-induced Brugada ECG Changes Associated With A Novel SCN5A Mutation In A Patient With Atrial Arrhythmias

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Background: Subclinical mutations in the genes associated with inherited arrhythmias may cause unexpected pharmacologic responses in antiarrhythmic therapies.

Methods: The administration of pilsicainide, a class Ic antiarrhythmic agent, caused marked Brugada-type ST-elevation and frequent PVCs in a 66-year-old Japanese male who had presented with paroxysmal atrial fibrillation and type I atrial flutter. The patient has structurally normal heart, with no family history of Sudden Cardiac Death (SCD) or syncope. Genetic screening using PCR/direct sequencing identified a novel *SCN5A* mutation, V1328M. Biophysical characteristics of WT and V1328M-*SCN5A* were studied using patch-clamp techniques.

Results: The whole-cell sodium current densities were comparable between WT and V1328M. While V1328M did not significantly affect the voltage-dependent activation kinetics, V1328M was found to rightward shift the voltage-dependency of the peak currents by 10 mV and the steady-state inactivation by 7 mV (inactivation V_h: WT, -100.2 ± 0.8 mV, n = 10; V1328M, -93.1 ± 0.7 mV, n = 10, $p<0.01$). The pharmacologic responses of WT and V1328M to pilsicainide were studied .Pilsicainide (25 μM) caused similar extent of the tonic block reduction of sodium currents induced by a low frequency pulse protocol (q15s) in WT and V1328M. On the contrary, V1328M significantly enhanced the use-dependent block (2Hz) by pilsicainide (25 μM) compared to the WT (%block: V1328M, 62.0 ± 1.7, n = 6; WT, 42.6 ± 1.0, n = 6, $p<0.001$). In addition, intracellular pilsicainide (500 μM) did not block both WT and V1328M currents.

Conclusion: Our findings suggest that a *SCN5A* mutation V1328M might predispose certain individuals in the antiarrhythmic pharmacotherapy to drug-induced Brugada ECG changes. Our data,also, suggests that the *SCN5A* mutation located in the intracellular side can affect the sodium channel blocking from the extracellular side.

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Inactivation In Kv1.4 Channels Involves Significant Intracellular Structural Rearrangements Mediated By A Proline Hinge

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Several voltage gated channel families share a common structural motif in the intracellular side of their S6 segment: a Proline-Valine-Proline sequence known as a proline hinge. We studied the proline hinge in Kv1.4 channels which activate and then inactivate via two distinct inactivation mechanisms, N- and C-type. We made several point mutations to the two prolines in the P-V-P hinge of Kv1.4 channels, most of which did not result in a functional channel. Two mutations did result in a functional channel: a glycine or alanine for the second proline. These mutations were studied in the presence and absence of the N-terminal to separate the effects on N and D-type inactivation (Kv1.4[P558A], Kv1.4[P558A]ΔN, Kv1.4[P558G], and Kv1.4[P558G]ΔN Both of these S6 mutations slowed or removed N- and C-type inactivation, and altered recovery from inactivation. The P558G mutation, which allowed more flexibility slowed N-type inactivation by nearly an order of magnitude and no C-type inactivation was observed in the abasensce of the N-terminal, consistent with our previous findings of a major structural rearrangement involving S6 in C-type inactivation. The P558A mutation was much more disruptive and slowed activation by more than an order of magnitude. No inactivation was observed in either N intact or deleted constructs, however activation in the presence of the N-terminal domain was biphasic and paradoxically slower for the P558A mutation. These results are consistent with our hypothesis that the proline hinge plays a significant role in inactivation and recovery, and that inactivation involves significant conformational changes of the intracellular side of Kv1 channels which is modulated by interaction with the lipophilic N-terminal ball and are closely linked with activation and deactivation.

3436-Pos Board B483

Cardiac Characteristics of a Mouse Model of Timothy Syndrome

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Timothy Syndrome (TS) is the only L-type Ca^{2+} channel (Cav1.2) defect linked to arrhythmias and sudden cardiac death (Splawski I et al. Cell 119: 19-31, 2004). Timothy SyTS results from a *de novo* gain-of-function mutation on the intracellular side of S6 from the first domain which affects the voltage dependent component of inactivation in Cav1.2 and results in prolongation of the QT interval.In addition to arrhythmogenesis, TS is associated with congenital heart disease, syndactyly and autism spectrum disorders. We created a knock-in mutation of TS in mice. Computer modeling suggested that the cardiac AP should be minimally affected under physiological conditions and in mice the arrhythmic potential should be observable only under pathophysiological conditions. The ECGs of conscious, unrestrained, unanesthetized mice and were performed double blinded. The QTc (38) in TS mice was prolonged, shifting from 44.3 ± 0.5 ms (n=8) for control mice to 47.2 ± 0.5 ms (n = 17) for mice expressing the TS mutation ($P<0.01$). Viewed qualitatively, many of the electrocardiograms from the TS mice showed a marked change in T-wave morphology. Other significant changes in conscious mice were also noted, the duration of the QRS complex shifted from 9.2 ± 0.4 ms (n=8) to 11.1 ± 0.2 ms (n = 17), heart rate showed a slight but not statistically significant increase and normalized heart rate variability showed a decrease from 5.1% ± 1.1 (n=8) to 2.6% ± 0.6 (n=17 $P<0.05$) indicating an increase in sympathetic tone in the TS mice. TS patients are particularly susceptible to arrhythmias in response